Reviewer’s report

Title: Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors

Version: Date: 30 November 2006
Reviewer: Sharon A McGrath-Morrow

Reviewer’s report:

General Review for “Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors.”

Raa et. al., In this study, the investigators used rats with DMBA-induced mammary tumors, and exposed them to hyperoxia, hyperbaric hyperoxia, or 5-FU. The effects of each treatment on tumor histology, apoptosis and size were assessed. The investigators also measured the relationship between tumor size and vessel density to determine the effects of treatment on vascular markers. They by gene expression profiling and RT-PCR that exposure to hyperoxia decreased glandular secretory proteins in rat mammary tumors. The investigators concluded that hyperoxia and moderate hyperbaric oxygen therapy alone can slow mammary tumor growth to a greater extent then 5-FU also in this animal model.

-------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. This study builds on their previous published article (Stuhr et.al., Cancer Letters, 2004) in which the investigators evaluated the effect of hyperbaric oxygen (HBO) at 2.0 alone or combined with 5-FU on mammary tumor size and vessel growth. The present manuscript analyzes the effects of HBO 1.5 and normobaric hyperoxia (100%) on growth of mammary tumors. They found a reduction in tumor size but far less then what they reported with HBO 2.0 alone or HBO 2.0 and 5-FU. Although their findings show slowing of tumor growth associated with a decrease in vessel density, the authors do not clearly state in the introduction why there are now studying the effects of HBO 1.5 and normobaric hyperoxia (100%) on mammary tumor growth. Did they have increased morbidity and mortality with using HBO 2.0 or HBO 2.0 + 5-FU on rats with mammary tumors and is this why they are now studying HBO 1.5 and normobaric hyperoxia in the same model. Rationalization for the use of the current study design should be elaborated in the introduction of the present manuscript.

2. The authors found down-regulation of glandular secretory proteins in tumors exposed to hyperoxia by gene expression profiling which was validated by RT-PCR. These genes included PSP, PIP and CSP1. It would be interesting to know if RNA expression of these genes is increased above baseline two weeks after treatment and if so do changes in gene expression correlate with increase in size of tumor growth.

3. The authors discuss at length the possible roles of HIF-1 and VEGF on tumor growth in their model and how hyperoxia may be inhibiting these genes, leading to decrease in tumor size and vessel growth and viability. It would add to the strength of the manuscript to demonstrate whether VEGF and/or HIF-1 expression is indeed decreased in tumors exposed to hyperoxia.

4. Does exposure to HBO 1.5 or normobaric hyperoxia cause any adverse effects to the lung of rats after completion of the 4 exposures?

-------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Figure 2 only shows the lung histology of normobaric hyperoxia treated tumor compared to control and not HBO 1.5 treated tumor, both should be shown since both are being discussed Also the figure legend doesn’t state when during treatment the depicted tumor example was taken.
2. Figure 4 doesn't add to the manuscript and should be removed.

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

'I declare that I have no competing interests'